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## Abstract

**Purpose:** The purpose of this study was to compare the effects of aerobic (AT) and combined aerobic and resistance training (CT) on blood pressure (BP), arterial compliance (AC), and left ventricular (LV) morphology in sedentary postmenopausal women with non-insulin dependent diabetes mellitus (NIDDM) as well as in subgroups of normotensive and hypertensive subjects.

**Methods:** Ten subjects performed AT (n=4) and CT (n=6) for 10 weeks. Graded exercise test, applanation tonometry, and echocardiography were completed prior to and following the treatment.

**Results:** BP, AC, and LV morphology were not altered after either exercise intervention. Following exercise, hypertensive patients decreased while normotensive increased LV mass index. Hypertensive diabetic women had reduced exercise capacity compared to a normotensive subgroup.

**Conclusion:** Ten weeks of AT or CT do not alter BP, AC, and LV morphology in postmenopausal diabetic women. LV morphology response to exercise in diabetic women depends on the coexistence of hypertension.

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*To my parents and brother*

*for their endless love and support*

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## List of Abbreviations

| | |
|---|---|
| AC | Arterial compliance |
| AT | Aerobic exercise (training) |
| BMI | Body mass index |
| BP | Blood pressure |
| CT | Combined aerobic and resistance exercise (training) |
| CVD | Cardiovascular disease |
| DBP | Diastolic blood pressure |
| $DBP_{60\ watts}$ | Diastolic blood pressure at a standard load of 60 watts |
| LV | Left ventricle |
| LVH | Left ventricular hypertrophy |
| LVIDd | Left ventricular internal cavity dimension in diastole |
| LVIDs | Left ventricular internal cavity dimension in systole |
| NIDDM | Non-insulin dependent diabetes mellitus |
| PWTd | Posterior wall thickness in diastole |
| PWTs | Posterior wall thickness in systole |
| RT | Resistance exercise (training) |
| RWT | Relative wall thickness |
| SBP | Systolic blood pressure |
| $SBP_{60\ watts}$ | Systolic blood pressure at a standard load of 60 watts |
| $VO_{2\ peak}$ | Peak oxygen consumption |
| $VO_{2\ 60\ watts}$ | Oxygen consumption at a fixed load of 60 watts |
| VSTd | Ventricular septal wall thickness in diastole |
| VSTs | Ventricular septal wall thickness in systole |

# Chapter 1

## Introduction

### 1.1 Purpose

The purpose of this investigation was to compare the effects of 10 weeks of aerobic (AT) and combined aerobic and resistance training program (CT) on systolic (SBP) and diastolic blood pressure (DBP) at rest, arterial compliance (AC), and left ventricular (LV) morphology in sedentary postmenopausal women with non-insulin dependent diabetes mellitus (NIDDM). This investigation also examined the effects of exercise on SBP, DBP, AC, and LV morphology in subgroups of normotensive and hypertensive postmenopausal diabetic women.

### 1.2 Significance of the study

Cardiovascular disease (CVD) is a leading cause of morbidity and mortality in women in developed countries (5,24). The risk of CVD increases after menopause and is further augmented in the presence of NIDDM and hypertension (5,29). In addition, the presence of cardiac and vascular abnormalities such as elevated LV mass (12,18,31), reduced AC (19,27), and coexistence of NIDDM and hypertension (29) further increases the risk of morbidity and mortality in diabetic and hypertensive individuals.

The effective control of the major cardiovascular risk factors, including NIDDM and hypertension, is essential from a public health perspective including primary and secondary prevention. The side effects and the financial burden imposed by the use of antihypertensive drugs have an impact on current treatment guidelines that emphasize the role of non-pharmacological interventions, including physical activity, in diabetic (3) and hypertensive patients (1). A major therapeutic goal in diabetic patients, particularly in the presence of hypertension, is to lower BP in order

to reduce the risk of CVD morbidity and mortality (1,29). However, cardiovascular events are directly related to the presence of structural and functional abnormalities in the cardiovascular system which implies that effective therapy should slow or reverse these changes. Exercise-induced BP reduction following AT is well documented in sedentary middle-aged hypertensive (2,8,15,17,26,30) and diabetic individuals (4,20,25,32) while the effects of RT on BP at rest are inconsistent (10,21,28). Beneficial outcomes of CT on reduction of BP at rest have been reported in middle-aged sedentary hypertensive men (16). Increased AC with a short-term AT has been found in men (7,23), but there is lack of similar information for women. Regression of left ventricular hypertrophy (LVH) with CT has been reported in older hypertensive men (16). Beneficial effects of RT on functional abilities and health status in elderly have been recognized recently (14). However, the effects of this type of training, either alone or in combination with AT, on BP, AC and LV morphology in postmenopausal women with NIDDM are not well known. In addition, a comparison of the BP, AC and LV morphology responses to exercise intervention in sedentary normotensive and hypertensive diabetic women has not been reported.

This investigation extends current knowledge of the effects of different training types, including CT, on SBP and DBP at rest, AC, and LV morphology in postmenopausal women with NIDDM.

From a practical point of view, the potential improvement in BP control and a positive impact of exercise on AC and LV morphology may decrease CVD morbidity and mortality in diabetic postmenopausal women, reduce costs to the health care system and enhance quality of life.

### 1.3 Scope of the Study

This study was limited to postmenopausal women (amenorrheic for at least 1 year), older than 50 years of age, with a clinically documented NIDDM (a fasting plasma glucose $\geq$ 6.7 $mmol \cdot L^{-1}$), absence of other chronic degenerative diseases and ECG abnormalities during a symptom-limited graded exercise test, and absence of orthopedic or musculoskeletal problems that might interfere with exercise. All subjects were sedentary for the preceding 6 months.

The intervention included 10 weeks of AT or CT, for 30 to 60 minutes, 3 times per week. AT consisted of 15 to 35 min of cycling at an intesity between 50% and 70% of heart rate reserve. RT included a warm-up set followed by 2 sets of 10 to 15 repetitions at 50% to 65% of 1 repetition maximum (1 RM) with one 1-minute rest between the sets.

Baseline and post-training measurements included oxygen consumption at a standard load of 60 watts and peak exercise; heart rate and BP at rest, at 60 watts power output, and peak exercise; and large and small AC. Echocardiographic measurements involved the following systolic and diastolic parameters: posterior wall thickness (PWTs, PWTd), ventricular septal wall thickness (VSTd) and internal cavity dimensions (LVIDs, LVIDd). LV mass is derived from the formula described by Devereux et al. (9) and normalized by body surface area.

### 1.4 Limitations

A major limitation of the present study is the small sample size because sedentary diabetic postmenopausal women represent an inconvenient population for initiation of and adherence to an exercise program. In addition, there is a possible overestimation of daily BP due to the elimination of any potential effects of post-exercise hypotension on BP measurements. Furthermore, the study does not include

ambulatory BP measurements to determine the effects of exercise on daily and nocturnal BP load. Another limitation may include absence of control of smoking and dietary habits, including alcohol and salt intake, although subjects were counseled at the initial testing not to change lifestyle behavior for the duration of the study. Finally, the study does not include a control non-exercising group since physical inactivity is considered a risk factor for the development of CVD (11).

### 1.5 Hypotheses

The primary hypothesis was that 10 weeks of CT would reduce SBP and DBP at rest to a greater extent than AT in postmenopausal women with NIDDM. The secondary hypotheses were: 1) both AT and CT would increase AC and regress left ventricular hypertrophy (LVH) in this population; 2) a subgroup of hypertensive diabetic women would demonstrate a greater decrease in SBP and DBP at rest in response to an exercise intervention than a subgroup of normotensive patients; and 3) AC and LV morphology response to an exercise intervention would be similar in diabetic women regardless of the presence or absence of hypertension.

### 1.6 Definitions

NIDDM is defined as a fasting plasma glucose $\geq 6.7$ mmol$\cdot L^{-1}$ (3).

Classification of BP levels is made according to the Sixth Report of the US Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (1). Mild hypertension (stage 1) is defined as SBP of 140 to159 mm Hg or DBP of 90 to 99 mm Hg. Moderate hypertension (stage 2) is defined as SBP of 160 to 179 mm Hg or DBP of 100 to109 mm Hg.

AC is defined as an absolute diameter (or area) change for a given pressure step at a fixed vessel length (22) and is inversely related to arterial stiffness. Capacitative AC represents a relationship between pressure fall and volume fall in the

arterial tree during the exponential component of diastolic pressure decay (22) and will be expressed as large AC. Oscillatory AC is defined as a relationship between oscillating pressure change and oscillating volume change around the exponential pressure decay during diastole (22) and will be expressed as a small AC.

LV mass index represents LV mass normalized by body surface area. LV hypertrophy in women is defined by a cut off value of 104 $g \cdot m^{-2}$ for a LV mass index (6).

Physical activity is defined as any bodily movement produced by contraction of skeletal muscle that substantially increases energy expenditure (13). Exercise (or exercise training) is defined as planned, structured, and repetitive bodily movement performed to improve or maintain one or more components of physical fitness (13). AT involves large muscle groups in dynamic activities that result in substantial increases in HR and energy expenditure (13). RT is designed specifically to increase muscular strength, power and endurance by varying the resistance, the number of times the resistance is moved in a single group (set) of exercise, the number of sets done, and the rest interval provided between sets (13).

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# Chapter 2

## Review of Literature

### 2.1 Introduction

Cardiovascular disease (CVD) is a leading cause of morbidity and mortality in women (8,105). The prevalence of CVD increases in postmenopausal women and is further aggravated in the presence of non-insulin dependent diabetes mellitus (NIDDM) and hypertension (8,120). In addition, the presence of cardiac and vascular abnormalities such as elevated left ventricular (LV) mass (42,69,135) and reduced arterial compliance (AC) (71,116), as well as coexistence of NIDDM and hypertension (120) further increases the risk of morbidity and mortality in diabetic and hypertensive individuals.

Due to the increased incidence of NIDDM (35) and hypertension (16) in sedentary individuals and the side effects and the financial burden imposed by use of antihypertensive medications, current treatment guidelines emphasize the role of non-pharmacological interventions including physical activity in both diabetic (3) and hypertensive patients (1). A major therapeutic goal in patients with NIDDM, particularly in the presence of hypertension, is to lower systolic (SBP) and diastolic blood pressure (DBP) in order to reduce the risk of CVD morbidity and mortality (1,120). However, effective therapy should also slow or reverse frequently present cardiovascular structural and functional abnormalities that are independently associated with an increased incidence of cardiovascular events in this population. This chapter reviews the role of exercise in the treatment of NIDDM and hypertension with a special emphasis on the effect of exercise on SBP, DBP, AC and LV morphology.

## 2.2 Non-Insulin Dependent Diabetes Mellitus

Diabetes mellitus is a major cause of disability and death in developed countries. According to the1996/97 National Population Health Survey, diabetes is ranked as the seventh leading cause of death in Canada (Health Canada, 2002). The prevalence of diabetes in Canada is estimated at 1.2 to 1.4 million (4.9% to 5.8% of the population aged 12 and over) including undiagnosed cases (Health Canada, 2002). NIDDM may account for 90% to 95% of all diagnosed cases of diabetes. Major risk factors associated with the development of NIDDM include older age, obesity, hypertension, a family history of diabetes, lower socio-economic status, and physical inactivity (3).

**Risk.** The mortality rate due to cardiovascular events is 2.4 and 3.5 times greater in diabetic men and women, respectively, than in general population (120). A number of factors contribute to a high prevalence of CVD in a diabetic population including hypertension, obesity, dyslipidemia, microalbuminuria, atherosclerosis, endothelial dysfunction, platelet hyperaggregability, coagulation abnormalities and "diabetic cardiomyopathy" (120).

**Common therapy.** Traditionally, treatment of NIDDM was focused on a diet and pharmacological therapy. Since an increase in insulin resistance with advancing age is mostly associated with age-related increases in body weight and physical inactivity, lifestyle modifications may play an important role in the treatment of these patients (85). The goal of treatment in NIDDM is to achieve and maintain near-normal blood glucose levels, optimal blood pressure (BP) (<130/85 mm Hg) and adequate lipid profile (3).

**Exercise.** Strong evidence of favorable acute and chronic effects of exercise in NIDDM subjects supports an important role of physical activity in the treatment of

this population (3,35,60,107). In fact, a sedentary lifestyle is associated with a 25% of incidence of NIDDM (35).

**Aerobic exercise.** Numerous studies suggest favorable effects of aerobic exercise (AT) in diabetic patients. Acute effects of AT include reduced blood glucose level and enhanced insulin-mediated glucose uptake by skeletal muscle (3). In addition, regular AT is associated with favorable changes in a lipid profile, functional capacity, body weight and body composition, and psychological well-being augmenting the quality of life of NIDDM patients (3,73,111,133).

**Resistance exercise.** Resistance exercise (RT) has been recommended in both primary and secondary prevention of CVD (100) due to various beneficial effects on functional ability and health status, particularly in elderly individuals (57). Regular RT is associated with improvements in muscular strength and endurance and bone mineral density (100). Some studies suggest that this type of training may increase coronary artery perfusion secondary to elevated DBP and decreased venous return (100). However, autoregulation of coronary artery perfusion is more complex and does not depend on changes in DBP only. Although controversy exists regarding the effect of RT on LV morphology in strength-trained athletes (130), no change in LV morphology and LV systolic function has been reported following 16 weeks of RT in healthy older men (52). In addition, this type of training may improve insulin sensitivity, glucose tolerance, glycemic control, and lipid profile in NIDDM patients (119). Potential mechanism for enhanced insulin sensitivity with RT in NIDDM patients may include favorable changes in body composition and increased muscle mass. In fact, insulin-mediated glucose uptake by skeletal muscle is directly related to the amount of muscle mass and inversely related to the amount of adipose tissue (3). Moreover, an addition of RT to AT provides a more comprehensive exercise program

for improvement of health and physical fitness in NIDDM patients (119). Finally, greater number of exercise modalities may enhance poor long-term adherence to an exercise program in this population (119).

**Exercise capacity.** NIDDM patients have impaired exercise capacity (104) and slower oxygen kinetics (103) compared to the healthy age-matched controls. Lower exercise capacity in these patients is also associated with a higher rate of diabetic complications such as diabetic neuropathy and retinopathy (36). Besides the presence of multiple cardiac risk factors including obesity, hypertension, older age, smoking, and physical inactivity (37), impaired exercise capacity in NIDDM patients may also be attributed to hyperglycemia, low capillary density, alterations in oxygen delivery, increased blood viscosity, presence of vascular and neuropathic complications, and genetic factors (3). Exercise intervention studies reported improved maximal exercise capacity (20,139) and oxygen kinetics in NIDDM patients (20). Interestingly, one study suggests that NIDDM patients tend to improve maximal exercise capacity to a greater extent than non-diabetic individuals (20).

**Exercise guidelines.** Current treatment guidelines for NIDDM patients emphasize a combination of AT and RT performed regularly at least 3 times per week (3,35). Recommended AT consists of a low-to-moderate intensity exercise (40-70% heart rate reserve) for at least 30 minutes daily and prolonged to 60 minutes if a weight loss is required (3,35). Recommendations for RT include use of lighter loads (50-80% of 1 RM) and higher number of repetitions (8-15) on 8-10 exercises with short rest intervals (3,35,119). The rate of progression of exercise programs in subjects with NIDDM should be slower due to frequently present advanced age, obesity, lower capillary density and increased percentage of type II fibers (3).

Although these results strongly support the use of exercise in the treatment of NIDDM patients, this treatment modality is currently underutilized probably due to lack of understanding and/or lack of motivation to exercise (3). Low compliance rates to exercise interventions longer than 3 months reported in NIDDM subjects represent a particular challenge in the treatment of this population (111).

### 2.3 Hypertension

Hypertension is one of the major risk factors for the development of CVD and is independently associated with congestive heart failure, stroke, renal disease, and all-cause mortality (1). Although a cause of essential hypertension remains unclear, a recent study suggests that increases of SBP may be at least in part attributed to the arterial and LV remodeling present in a hypertensive population (114).

**Risk factors.** Major risk factors for hypertension are smoking, dyslipidemia, diabetes mellitus, age older than 60 years, sex (male and postmenopausal women), African-American race, family history of CVD for women under age 65 and men under age 55, obesity, salt intake, alcohol consumption, and physical inactivity (1). Presence of multiple risk factors further exacerbates the risk of the development of hypertension (128).

**Hypertension in women.** Besides the major risk factors listed above, oral contraceptives are another important cause of elevated BP in women (101). The prevalence of hypertension in women increases with advancing age, particularly after menopause and may be attributed to obesity, sedentary lifestyle and increased alcohol intake, while the impact of estrogen reduction is currently unresolved (6). Beneficial effects of estrogen involve systemic vasodilation which is associated with increased cardiac output and reduced vascular resistance in hormone replacement therapy users

(53). Although some research has suggested gender specific treatment of hypertension (72), current evidence does not support that hypothesis (6).

**Goal.** The goal of prevention and treatment of elevated BP is to reduce associated morbidity and mortality (1). While an optimal BP in uncomplicated hypertension is below 140/90 mm Hg, recommended target BP in diabetic patients is even lower (<130/85 mm Hg) (1).

**Common therapy.** Treatment of elevated BP includes both pharmacological and non-pharmacological interventions (1). Current guidelines recommend that non-pharmacological therapy should always be initiated prior to or as an adjunct treatment to the pharmacological intervention (1). A non-pharmacological intervention should include proven lifestyle modifications: weight reduction in obese individuals, moderation of alcohol intake, increased aerobic physical activity, moderation of dietary sodium, adequate intake of potassium, calcium and magnesium, smoking cessation, and reduction of dietary saturated fat and cholesterol intake (1). Although exercise and diet interventions are the most frequently used non-pharmacological therapies for BP reduction, their antihypertensive effects are not additive (45). In addition, moderate exercise-induced BP reduction may be inadequate to achieve optimal BP levels in patients with moderate to severe hypertension and additional pharmacological therapy is frequently required (31). Lifestyle modifications should be particularly encouraged in patients with additional CVD risk factors such as abnormal lipid profile and NIDDM (1).

**Exercise.** Studies have reported an inverse relationship between physical activity and physical fitness and the risk of development of hypertension in both genders (16,102,122). The protective effects of exercise on overall mortality rates are

associated with recent and current physical activity that further emphasize the importance of regular physical activity in this population (115).

**Exercise guidelines.** Current treatment guidelines for hypertensive patients recommend AT performed 3 to 5 times per week, at low to moderate intensity (50% to 80% of maximal heart rate), 30 to 60 min per session (35,68). Intermittent exercise (3 to 4 times per day at least 10 min) is recommended for patients who are unable to sustain longer exercise periods (68). Low intensity, high volume (12 or more repetitions) RT is recommended as a complement to the aerobic component (68). The rate of exercise progression should be adjusted to the patient's needs and abilities (68).

### 2.4 Coexistence of Non-Insulin Dependent Diabetes Mellitus and Hypertension

Frequently observed co-existence of NIDDM and hypertension represents a particularly high risk for the development of CVD (9,85,108,127). Recent data suggest that up to 75% of CVD in a diabetic population may be attributable to hypertension (120). Diabetic patients are more prone to develop hypertension than non-diabetic individuals (120). On the other side, a higher prevalence of diabetes mellitus has been reported in hypertensive than in normotensive patients (120).

**Mechanisms.** Suggested underlying mechanisms for an association between NIDDM and hypertension is/are insulin resistance and/or hyperinsulinemia (13). Insulin has both short- and long-term effects on promoting and sustaining an increase in BP. Short term effects consist of arterial vasodilatation, sympathetic nervous system stimulation, and sodium retention (15). Long-term effects include altered cation transport and proliferation of vascular smooth muscle cells (15,48). Since an increase in insulin resistance with advancing age is mostly associated with age-related

increases in body weight and physical inactivity, lifestyle modifications play an important role in the treatment of these patients (85).

**Treatment.** Treatment of coexisting NIDDM and hypertension is the same as the treatment for hypertension with a primary goal to lower BP and a secondary goal to treat all CVD risk factors (85). The goal of antihypertensive interventions in this population is to achieve and maintain BP below 130/85 mm Hg in order to markedly reduce the risk of CVD morbidity and mortality (1,108).

### 2.5 Blood Pressure and Exercise

Over the past 2 decades, numerous studies have documented an exercise-induced SBP and DBP reduction in both normotensive and hypertensive individuals (138). However, limited data are available in women, diabetic patients, and patients with co-existence of NIDDM and hypertension.

Both acute and regular exercise reduces BP at rest in hypertensive patients. Post-exercise hypotension has been reported in hypertensive men following a bout of low to moderate intensity AT (98). Numerous studies have reported reduction of SBP and DBP at rest (2,23,26,45,49,59,62,63,83,91,106,112,124,129,140) and during exercise (63,91,106,112) following an exercise intervention in sedentary hypertensive individuals. Since both resting and exercise BP return to prior values within 3 months of cessation of exercise (106), regular physical activity in hypertensive population should be encouraged.

**Aerobic exercise.** AT has been proven as an effective means for BP reduction in hypertensive patients of both genders (2,26,45,49,50,59,63,67,91,98,112,124) with an average reduction between -8 to -10 mm Hg for SBP and -7 to -8 for DBP (68). Several AT intervention studies performed on diabetic patients reported a SBP reduction of –5 to –11 mm Hg and DBP reduction of 0 to –8 for DBP (7,73,111,139).

In addition, 3 months of AT reduced BP at a fixed exercise load (e.i.100 watts) by -26/-7 mm Hg in middle-aged diabetic patients of both genders (111). Effect of exercise on SBP and DBP at rest and during exercise in post-menopausal diabetic women in these studies were confounded by the presence of male data (7,33,56,73,111).

**Resistance exercise.** Traditionally, it was believed that RT is associated with excessive BP elevation and was not recommended in hypertensive patients. However, recent studies suggest that RT can be performed without complications in hypertensive individuals. BP responses during RT performed at intensity of 40% to 60% of 1-repetition maximum (1 RM) in cardiac patients do not exceed BP response observed during an aerobic session (19).

Effects of RT on BP at rest are not consistent. Some (83), but not all studies (17,33,34,51,56,118) have found a reduction in BP at rest following RT intervention in healthy individuals with high-normal BP (23,83), middle-aged patients with impaired glucose tolerance (34), NIDDM (33,56), hypertension (51) and multiple CVD risk factors (118). Circuit RT in one study failed to demonstrate change in BP at rest in hypertensive individuals (51) while BP reductions in the other study were similar to the reductions observed in an aerobic and control group (17). A recent study has reported that 6 months of high intensity RT reduces BP at rest in healthy older subjects with high normal BP (83). These findings suggest that a higher intensity of RT may be necessary to induce beneficial effects on BP in hypertensive patients. Two studies that examined the effects of circuit RT in middle-aged (33) and older (56) NIDDM patients failed to demonstrate a reduction in BP at rest following 3 and 5 months of RT , respectively.

Studies comparing the effects of AT and RT on SBP and DBP at rest failed to find a difference between the two treatments in healthy older individuals (23), middle-aged hypertensive patients of both genders (17) and middle-aged men with coronary heart disease risk factors (118). Seven-point decrease in SBP and six-point decrease in DBP following 16 weeks of RT in hypertensive patients in one study were not significantly different from changes observed in a control group (17).

Due to inconsistent results of this training modality on SBP and DBP at rest, RT is not recommended as a primary form of exercise in hypertensive patients but only in addition to AT (68). Beneficial effects of combined aerobic and resistance training (CT) on BP reduction have been reported in middle-aged sedentary hypertensive men (62) while no similar study has been reported in women.

**Exercise interventions in postmenopausal women.** Research about the effects of exercise on BP in postmenopausal women is limited. Four studies have reported SBP and DBP reduction following an AT intervention in hypertensive women (26,59,106,112). The range of BP reduction for hypertensive (17,23,45,49,124,140) and diabetic (139) women reported in several other studies was confounded by the presence of male data. BP reduction has also been reported after 6 months of heavy RT in healthy older women with high normal BP (83). CT has been found to prevent muscle atrophy associated with aging in normotensive older women without compromising cardiovascular adaptations (40). However, no study has reported the use of RT, either alone or in combination with AT, in the treatment of diabetic and/or hypertensive postmenopausal women.

**Magnitude of BP reduction.** The extent of exercise-induced BP reduction depends on the initial BP level (31), duration and intensity of exercise (31), age (59), gender (50), and a family history of hypertension (91). In addition, the absolute

benefits of antihypertensive therapy, including exercise, depend on the presence or absence of additional CVD risk factors and preexisting clinical CVD or target organ damage (94). Patients with the highest initial SBP achieve the largest reductions in BP following an exercise intervention (31). Most studies have demonstrated reductions in BP at rest following 8 to 12 weeks of AT, while longer exercise interventions have provided inconsistent results probably due to lower compliance rates (49,63,67,106,112,138). A recent meta-analysis of randomized controlled trials has found similar BP reductions with low and moderate intensity AT (39). This finding is important from both a clinical and practical point of view since low intensity AT is associated with a reduced risk of injury and cardiovascular complications, absence of side effects, low cost, and feasibility for most patients (67). Older hypertensive patients reduce BP to a lesser extent compared to younger hypertensive individuals (59). Recent reviews suggest that women tend to reduce BP to a greater extent in response to an exercise intervention than men (50,68). Finally, exercise-induced BP reductions are more pronounced in patients without than with a family history of hypertension (91).

**Mechanisms.** The underlying mechanisms for an exercise-induced reduction in SBP and DBP at rest and during exercise observed in previous studies remain unclear. Postulated mechanisms are likely multi-factorial and depend on the nature of hypertension and the individual's clinical characteristic (31). As discussed above, the absolute benefits of antihypertensive therapy, including exercise, depend on the initial BP level, presence or absence of additional CVD factors and target organ damage (94). Exercise-induced reduction in BP is ultimately associated with reduced total peripheral resistance, cardiac output, or both (68). One of the postulated mechanisms includes increased vascular vasodilation attributed to increased arterial compliance

and/or improved endothelial function (31,63). Improvement in reactive hyperemia, an index of endothelium-dependent vasodilation, following AT intervention was demonstrated in hypertensive patients and was accompanied with significant reduction in BP (54). Another speculated mechanism includes an attenuated activity of sympathetic nervous system in a trained state (31). Reduced plasma norepinephrine levels were found following an AT intervention in the older hypertensive patients (49). Finally, changes in BP may reflect changes in insulin sensitivity and hyperinsulinemia (31). In older hypertensive individuals with abdominal obesity and insulin resistance syndrome, it is likely that exercise- or weight loss-induced reduction in insulin resistance and hyperinsulinemia may contribute to BP reduction (27). This finding may explain a lower incidence of insulin resistance syndrome in physically active individuals. Some studies speculate the possible role of decreased plasma volume (68) and increased skeletal muscle capillary bed (63), but more data are required to support these mechanisms. Further studies are needed to define underlying mechanism of hypotensive effects of exercise.

Strong evidence suggests that regular AT has beneficial effects on SBP and DBP at rest in normotensive, hypertensive, and diabetic patients. However, there is a paucity of research in postmenopausal women. The outcome of AT and/or CT in postmenopausal women with NIDDM and/or hypertension has not been reported. CT have beneficial effects on cardiovascular adaptations and muscle atrophy prevention associated with aging in normotensive older women (40). The enhanced health benefits associated with this type of training should be examined in diabetic and/or hypertensive postmenopausal women as well since maintaining muscular strength and endurance in older women is a critical health and a quality of life factor.

### 2.6 Arterial Compliance

AC is defined as an absolute increase in artery diameter for a given rise of pressure and is inversely related to arterial stiffness (22). AC reflects the function of the vascular system to convert central pulsatile into peripheral continuous blood flow (84). Decreased large artery compliance is associated with a reduced stroke volume storage that decreases DBP and impairs coronary perfusion, while increases SBP and hence augments LV afterload and myocardial oxygen demand (11). In addition, arterial stiffness is accompanied with an increased pulse wave velocity resulting in an earlier return of the reflected pulse waves, and further increase in central systolic BP (25,79). Finally, augmented SBP impairs diastolic and systolic myocardial function and may be a potent stimulus for the development of left ventricular hypertrophy (LVH) (79).

**Risk.** Decreased AC is an independent predictor of cardiovascular and all-cause mortality in both diabetic (116) and hypertensive patients (71) and is associated with LVH, congestive heart failure, aortic root regurgitation, and orthostatic, postprandial and isolated hypertension (126).

**Causes.** Increased arterial stiffness may be a passive consequence of elevated BP or a result of structural and functional alterations in the arterial wall (79). Reduced AC in small arteries in early stages of hypertension may be caused by a recruitment of collagen fibers at lower distending pressures compared to the normotensive state (58). However, later in the disease, small AC may be reduced at least in part due to structural alterations in arteries such as reduced artery diameter, increased collagen-to-elastin ratio, cross-linking of collagen fibers and resulting tension of the collagen network at earlier portions of the pressure curve (58). An impact of endothelial

function and endothelium-derived nitric oxide on the elasticity of arteries in humans have been recognized recently (66).

**Aging.** Major factors contributing to arterial stiffness are aging and hypertension (11). Age-related changes include elastin degradation, calcium deposition, increased arterial diameter, smooth muscle cell hypertrophy and increased collagen accumulation and cross-linking (11,61,79). These changes may be attributed to tissue fatigue that is a consequence of the repetitive cyclic stress on elastin fibers which, over time, causes fracture and separation of the fibers, followed by arterial wall stretching and remodeling (11,79,93).

However, the effect of aging on AC is not uniform. A reduction in central but not peripheral AC with advancing age in both genders may be attributed to the different roles of central and peripheral arteries in hemodynamic regulation (12,125). Central arteries are exposed to a greater pulsatile load due to a cushioning function, and, therefore, are more susceptible to deterioration of elastin fibers (125). In addition, gender differences in a response of AC to aging have been found and may be attributed to hormonal and constitutional factors (132). Estrogen replacement therapy may have a protective effect on age-related alterations in arterial structure and function in postmenopausal women (84). Although a large artery response to hypertension has a genetic component, age-related changes are accelerated in the presence of hypertension and a high salt intake (11,12,93).

**Hypertension and NIDDM.** Decreased AC has been reported in hypertensive (87) and diabetic patients (4,86). Hypertension is associated with hypertrophy and collagen accumulation in the vessel wall and may be related to an increased mechanical stress and/or increased activity of trophic humoral factors (11). Different adaptive changes are found in small and large arteries in response to elevated BP.

Arterial remodeling of small arteries is associated with a reduced internal diameter and increased wall thickness to internal diameter ratio that increases peripheral resistance and further magnifies hypertension (5). Large arteries respond to high BP by increasing wall thickness and no change or increase in the internal diameter (11). Reduced AC in diabetic patients has been reported recently (4) and may be associated with a reduced ability of insulin to regulate endothelial function (86,121). The greatest degree of arterial stiffness is found in individuals with both hypertension and NIDDM that places these patients in a particularly high-risk group for cardiovascular events (9).

**Exercise.** Greater total systemic AC is associated with a higher level of physical activity in healthy men (21,65). Although attenuated, age-related decreases in AC are found in physically active men (126), but not in physically active normotensive women (113,125). Positive linear correlation has been reported between changes in total systemic AC and exercise capacity in both genders (21,125). Possible mechanisms by which regular exercise may prevent an age-related decrease in AC may include an attenuated increase in BP, reduced age-related structural changes in arterial walls, and/or maintenance of endothelial function (125). Endurance-trained and recreationally active healthy older individuals have increased AC by 40% and 17%, respectively, compared to their sedentary peers (126).

Both acute (64) and chronic AT (21,126) increases AC and may induce large artery remodeling (30) in healthy male subjects. One study reported an increased AC by 25 % in previously sedentary middle-aged and older healthy men following 12 weeks of AT intervention (126). Another study found increased total systemic AC following 4 weeks of AT in young men (21). Decreased both central and peripheral AC have been reported in young healthy men who participate in long-term RT

without an aerobic component (14). Possible mechanisms for this finding remain unclear. The effects of an exercise intervention on AC in diabetic and hypertensive women have not been examined.

**Mechanisms.** Several mechanisms have been suggested for increased AC observed with regular exercise. One of the mechanisms involves increases in pulse pressure and mechanical distension during exercise that may exert a "stretching" effect on collagen fibers in the arterial wall and modify some of the connective tissue cross-linking (61,126). Another postulated mechanism includes exercise-induced increases in laminar blood flow and shear stress that may enhance endothelium-dependent vasodilation by up-regulating nitric oxide synthase and increasing the release of nitric oxide and prostacyclin (44,92). This mechanism may also be responsible for increased AC demonstrated after an acute bout of exercise (64). Several studies reported that exercise improves baroreflex sensitivity, a parameter that is strongly and positively related to AC (65,88,89). Finally, regular exercise may produce sympathoinhibitory effects either directly or by enhancing nitric oxide production that modulates the smooth muscle cell tone in the arterial wall (126).

Effects of exercise on AC in sedentary postmenopausal women remain to be determined. Studies have shown that menopause and hormone replacement therapy have an independent effect on endothelial function (76,123) and therefore may influence AC. These results suggest that data obtained on male populations may not necessarily be generalized to women.

### 2.7 Left Ventricular Morphology

LV morphology can be modified by altered hemodynamics and ventricular loading conditions caused by either exercise or a chronic SBP elevation (96). Left ventricular hypertrophy (LVH) is an adaptive mechanism by which the heart

normalizes wall stress and preserves LV systolic function in early stages of hypertension (74). Over time, LVH leads to LV diastolic and systolic dysfunction, and may lead to heart failure (46). Besides LVH, clinical presentation of the hypertensive heart disease includes cardiac arrhythmias, ischemic heart disease, diastolic dysfunction, and congestive heart failure (41,74).

**Physiologically vs. pathologically increased LV mass and wall thickness.** Increased LV mass and LV wall thickness have been reported in some competitive endurance- and strength-trained athletes (38,80,96,131). However, most athletes have normal LV geometry and the term LVH should be used with caution in this population (38). Exercise-induced alterations in LV geometry are not associated with an impairment of LV diastolic and/or systolic function (96) and are entirely reversible after cessation of exercise stimuli (32). Hence, a relationship between heart dimensions and ergometric performance may be used as a criterion for differentiation between physiologically and pathologically increased LV mass and wall thickness (130).

**Left ventricular mass.** Increased LV mass is associated with an augmented risk for cardiovascular events and all cause mortality in hypertensive patients (69). An adverse prognostic outcome is apparent in both genders, but more pronounced in women (110).

In the general population, LVH is present in 16% of middle-aged men and 19% of middle-aged women (75). However, the prevalence increases with aging and hypertension in both genders (75). A greater age-related increase in prevalence of LVH in women compared to men (75) may be attributed to the effects of menopause. Structural and functional manifestations of hypertensive heart disease have been found in postmenopausal women regardless of BP level (109). This finding supports a

role of estrogen reduction as an important determinant of early cardiac changes after menopause. However, an impact of hormone replacement therapy on LV mass and function in postmenopausal women is not presently clear (53). Increase in LV wall thickness after menopause has been reported regardless of BP level and estrogen supplementation (99,109). In hypertension, the prevalence of LVH increases from 12 to 20% in mild to 50% in more severe cases (41) and is highly dependent on BP level achieved during the treatment which further emphasizes the importance of adequate BP control in this population (24).

**Left ventricular geometry.** The LV may respond to altered systemic hemodynamics and ventricular loading conditions with different geometric patterns (43). According to the LV mass index (LV mass divided by body surface area) and relative wall thickness, four different LV geometric patterns are defined (41). Concentric LVH represents an adaptation to an increased pressure overload and is characterized by an increase in both relative wall thickness and LV mass. Eccentric LVH develops in response to volume overload and is identified by normal relative wall thickness and elevated LV mass. Concentric remodeling is characterized by increased wall thickness and normal LV mass. Normal LV geometry is diagnosed in absence of increases in either LV mass or relative wall thickness. LV geometric patterns are defined by cut off values of 116 $g \cdot m^{-2}$ for men and 104 $g \cdot m^{-2}$ for women for LV mass index, and 0.43 for relative wall thickness (10). The highest risk for CV events is associated with concentric hypertrophy, intermediate with concentric remodeling and eccentric hypertrophy, and lowest with normal LV geometry (69).

**Hypertension.** The majority of hypertensive patients have normal LV geometry. However, in hypertensive patients with abnormal LV geometry, higher prevalence of eccentric than concentric LVH has been reported (24,43). Eccentric

hypertrophy and concentric remodeling in one study were present in 27% and 13% of untreated hypertensive patients, respectively, while concentric hypertrophy was detected in only 8% of the patients (43). A recent study suggests that stroke volume and the degree of arterial stiffness in hypertensive patients may be stimuli to the different LV geometric patterns (10). The same study found that hypertensive patients with concentric remodeling have lower stroke volumes, while those with eccentric LVH have higher stroke volumes than reference adults (10). A higher degree of arterial stiffness in the same study was associated with concentric remodeling than with eccentric hypertrophy (10). These results support the hypothesis that increased prevalence of concentric LVH in patients with co-existent hypertension and NIDDM can be at least in part responsible for increased CVD risk in this population (9).

Although one study suggested that both LV mass and geometry should be considered in a risk stratification of hypertensive subjects (69), more recent studies have found that different LV geometric patterns in hypertensive individuals provide little additional prognostic information compared to LV mass only (110,137). However, recent findings that hypertension is more strongly associated with increased LV mass, while diabetes has more pronounced impact on LV relative wall thickness (9) warrant reexamination of a prognostic importance of both LV mass and geometry in patients with co-existence of both diseases.

**NIDDM.** NIDDM accelerates the development of LVH in hypertensive patients and increases the risk of CV morbidity and mortality in that population (47). In addition, presence of diabetic cardiomyopathy that is characterized by early LV diastolic dysfunction and late systolic impairment (82) significantly contributes to CVD morbidity and mortality in diabetic population, particularly in patients with coexistent hypertension (120). NIDDM is independently associated with increased LV

wall thickness and mass, reduced LV systolic function, and reduced AC (29). Coexistence of hypertension and NIDDM further increases prevalence of LVH and aggravates LV diastolic and systolic function in comparison to either disease alone (9,28,78,95). The effect of diabetes on LV mass is augmented through an interaction with advancing age and obesity (70).

**Treatment.** Both pharmacological and non-pharmacological interventions may produce favorable effects on LV mass in hypertensive individuals. Although all antihypertensive drugs have a potential to reduce LV mass, ACE inhibitors are currently considered the most effective pharmacological treatment (77). However, lifestyle modifications such as weight reduction and exercise may also be effective (55,67,81).

To date, four studies reported effects of an exercise intervention on LV morphology in sedentary middle-aged and older hypertensive men. One study reported that a 12-week weight-reduction program consisted of a combined mild exercise and mild hypocaloric intake reduces body weight and LV mass in both normotensive and hypertensive obese middle-aged individuals (55). These changes were associated with a significant reduction in SBP, DBP, and mean BP in a hypertensive subgroup. Other studies reported a decrease in LV mass index following 4 and 7 months of AT (67,129) and an increase in LV mass index without concomitant alteration in diastolic function following 10 weeks of CT (62). In addition, decrease in interventricular septal thickness (67,129), posterior wall thickness (129) were reported following AT while no change was observed following CT (62). CT decreased LVIDd but increased LVIDs in these patients (62). The effects of AT and CT on LV geometry have not been studied in diabetic and hypertensive women.

**Regression of left ventricular hypertrophy.** Regression of LVH should be considered as an important target of antihypertensive therapy (134) because benefits include a reduced risk for the development of CVD, improved LV filling, and reduced incidence of myocardial ischemia, lethal cardiac arrhythmias, and possibly sudden death (32,136). The extent of LVH regression depends on the efficacy and duration of BP control, pretreatment LV mass, and activation or deactivation of cardiac trophic factors (24). Optimal control of both ambulatory and clinical BP (BP <140/90 mm Hg, or <130/85 mm Hg in subjects with NIDDM) plays an important role (24,117). An aggressive treatment is recommended for individuals who fail to achieve LV mass reduction following a pharmacological intervention (136).

**Left ventricular morphology and arterial compliance.** Recent data suggests a correlation between LVH and reduced AC and/or presence of atherosclerosis. Decreased AC accompanied by aging and hypertension may be a potent stimulus for the development of LVH (10,53). The underlying mechanism may be an increased LV afterload due to a greater increase in central compared to peripheral SBP caused by arterial stiffening (82). Parallel changes in the structure and function of the common carotid artery and the geometric patterns of the LV have been reported in hypertensive patients (18). Decreased common carotid AC is associated with concentric hypertrophy and remodeling, while an increased artery diameter parallels increased LV cavity size in that population (18). This is in agreement with the results of another study that the degree of arterial stiffening may have an impact on the development of concentric LVH in hypertensive subjects (10).

More recently, the importance of endothelial function in the incidence of cardiovascular events has been recognized (90). An inverse relationship exists between LV mass and endothelium-dependent vasodilatation in hypertensive subjects

(97). More severe endothelial dysfunction associated with concentric LVH may be a potential link for an increased incidence of cardiovascular events in patients with that LV geometric pattern (97). Future studies need to clarify an interaction among endothelial function, AC and LV geometry in NIDDM and hypertension.

### 2.8 Summary

Current treatment guidelines for NIDDM and hypertension emphasize the role of regular physical activity. However, information about the effects of regular exercise on SBP and DBP at rest, AC and LV morphology in postmenopausal diabetic women is lacking. Recent studies demonstrated BP reductions following AT intervention in middle-aged diabetic patients of both genders. Several studies reported increased AC following AT intervention in sedentary healthy men. AT and CT demonstrated a positive impact on SBP, DBP, and LV morphology in hypertensive men. No study has reported the use of RT, alone or in combination with AT, in the treatment of diabetic women. CT has been found to prevent muscle atrophy associated with aging in normotensive older women and may increase muscle mass and positively affect the NIDDM. Finally, frequent coexistence of hypertension and NIDDM in postmenopausal women emphasizes the importance of clarifying the effects of exercise in that population. Future studies need to extend the knowledge of the health-related outcomes of different training modalities on SBP and DBP at rest, AC and LV geometry, in postmenopausal women with NIDDM.

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# Chapter 3

## Effects of Aerobic and Combined Aerobic and Resistance Training on Systolic and Diastolic Blood Pressure, Arterial Compliance, and Left Ventricular Morphology in Sedentary Postmenopausal Women with Non-Insulin Dependent Diabetes Mellitus

### 3.1 Introduction

Non-insulin dependent diabetes mellitus (NIDDM) is a strong risk factor for cardiovascular morbidity and mortality in women (6), particularly in hypertensive patients (58). Increased incidence of NIDDM and hypertension in postmenopausal women may be at least in part attributable to sedentary lifestyle (20). As a result, current treatment guidelines emphasize a role of regular physical activity in both diabetic (3) and hypertensive individuals (1).

Strong evidence suggests that aerobic exercise (AT) is an effective means for reducing systolic (SBP) and diastolic blood pressure (DBP) at rest in sedentary middle-aged diabetic (5,38,53,65) and hypertensive patients (2,14,27,32,54,59). The effects of resistance exercise (RT) on blood pressure (BP) reduction remain equivocal (9,19,23,26,40,56). As a result, RT is not currently recommended as a primary form of exercise in hypertensive patients (36). However, due to the beneficial effects on functional and health status as well as metabolic profile, this training modality is frequently recommended for diabetic patients (57) and for older adults whose functional status is compromised by muscle atrophy (3,48). Favorable effects of combined aerobic and resistance training (CT) on BP reduction have been reported in middle-aged sedentary hypertensive men (30) while no similar study has been done on diabetic women. CT is also gaining popularity for diabetic patients since increasing skeletal muscle mass could increase an available glucose storage area,

thereby facilitating glucose clearance from the circulation and reducing the amount of insulin required to maintain a normal blood glucose levels (28).

Decreased arterial compliance (AC) is an independent predictor of cardiovascular and all-cause mortality in diabetic patients (55). Positive linear correlation was found between changes in total systemic AC and exercise capacity in both genders (11,60). Several studies reported increased AC following both acute (33) and chronic AT (11,61) in healthy men, but there is lack of similar information for women.

Elevated left ventricular (LV) mass increases the risk of morbidity and mortality in diabetic patients (37). Recent studies reported a decrease in LV mass in response to AT (35,63) and an increase in LV mass without concomitant alteration in diastolic function following CT (30) in sedentary middle-aged and older hypertensive men. Effects of exercise intervention on LV mass in diabetic women remain to be determined.

The purpose of this study was to compare the effects of 10 weeks of AT and CT on SBP and DBP at rest, AC, and LV morphology in sedentary postmenopausal women with NIDDM. In addition, the study examined the effects of exercise on SBP, DBP, AC, and LV morphology in subgroups of normotensive and hypertensive postmenopausal diabetic women. The primary hypothesis was that 10 weeks of CT would reduce SBP and DBP at rest to a greater extent than AT in postmenopausal women with NIDDM. The secondary hypotheses were: 1) both AT and CT would increase AC and regress left ventricular hypertrophy (LVH) in this population; 2) a subgroup of hypertensive diabetic women would demonstrate a greater decrease in SBP and DBP at rest in response to an exercise intervention than a subgroup of normotensive patients; and 3) AC and LV morphology response to an exercise

intervention would be similar in diabetic women regardless of the presence or absence of hypertension.

### 3.2 Methods and Procedures

**Subjects.** Sixteen sedentary postmenopausal women with NIDDM were recruited from the Metabolic Unit within the University of Alberta Hospitals. Inclusion criteria were: self-reported postmenopausal status (amenorrheic for at least 1 year); 50 to 70 years of age; a clinically documented NIDDM (a fasting plasma glucose $\geq 6.7$ mmol·$L^{-1}$); absence of other chronic degenerative diseases, except LVH (based on medical history, physical examination, and resting and exercise electrocardiography), absence of orthopedic or musculoskeletal problems that may interfere with exercise, and sedentary during the preceding 6 months. Subjects were instructed to maintain all other elements of their usual lifestyle and dietary habits during the study. Participants who are taking antihypertensive medications continued with their prescribed drug therapy during the period of the study. All subjects completed a physical examination by a physician to identify any subjects who may be at risk from the participation in the study. The subjects were informed of the possible risks and discomfort that may result from participation and signed an informed consent. Ethical approval for this study was obtained from the University of Alberta, Biomedical Ethics Committee for human experimentation.

**Research design.** Eligible patients were randomly assigned to an AT group or CT group. The subjects were tested at the baseline and following 10 weeks of an exercise intervention. Measurements included oxygen consumption, heart rate and BP at a standard load (60 watts) on a cycle ergometer and oxygen consumption at peak exercise ($VO_{2peak}$). Heart rate, SBP, and DBP at rest were obtained simultaneously with large and small AC data assessed by an applanation tonometry procedure. Two-

dimensional echocardiographic measurements included the following measures: posterior wall thickness (PWTs, PWTd), ventricular septal wall thickness (VSTs, VSTd) and internal cavity dimensions (LVIDs, LVIDd). LV mass was calculated by the Devereux formula (16) and normalized by body surface area.

**Exercise testing.** An incremental exercise test with expired gas collection was performed on an electrically braked Monark cycle ergometer. Following 2 minutes of rest, the exercise intensity was increased every 2 min by 15 W until volitional exhaustion. Frequency of pedaling was individually adjusted to 40-80 rpm and maintained at a consistent level throughout the test. During the test, expired gas was analyzed continuously for $O_2$ and $CO_2$ using standard techniques of open circuit spirometry. A standard 12-lead ECG was recorded prior to, and continuously throughout the graded exercise test for safety purposes and detection of the presence of ischemic heart disease. The test was stopped if abnormal ECG tracing suggesting a presence of cardiac abnormalities. SBP, DBP, heart rate and the Borg rating of perceived exertion were recorded at the end of every exercise stage. The metabolic cart (Medgraphics, St. Paul, Minnesota) was calibrated before and after every test.

Subjects randomized to the CT group performed a one repetition maximum (1 RM) strength testing at baseline to determine an individual training prescription. The testing was performed on the following eight exercises: leg press, leg extension, leg curl, chest press, shoulder press, lat pull-down, arm curls and triceps pushdown. Following a warm up set of 10 repetitions, a weight was increased and number of repetitions decreased until a subject could perform only one repetition with a proper form. On average, subjects completed 5 sets before 1 RM was determined. One minute of rest was allowed between the sets.

Training intensity was individually determined based on initial testing results. All post-intervention measurements were performed at least 24 to 48 h after the last exercise session to avoid the immediate effects of a single bout of exercise (47).

**Applanation tonometry.** AC was assessed on the right radial artery using computerized arterial pulse waveform analysis (Hypertension Diagnostics Inc (HDI)/*PulseWave*™, Eagan MN). A commercially available instrument equipped with a pencil-shaped probe was placed on the skin over the artery. The use of the probe is based on the principle of applanation tonometry which states that flattening of the curved surface of a pressure-containing structure balances the circumferential wall stress of the structure and allows accurate registration of the pressure within the structure (31). The radial artery is ideal for applanation tonometry because it is easily accessible and well supported by a bone structure (45). Following 5 min of rest in the upright sitting position, signal averaged pulse waves were recorded for 30 seconds and calibrated against the automatically measured brachial BP on the other arm. SBP and DBP measured during this procedure was used as BP at rest. The diastolic decay of the waveform is analyzed mathematically and capacitive (large) and oscillatory (small) AC were calculated based on a modified Windkessel model of circulation (13). Special attention was devoted to the positioning and angulation of the tonometer, amount of the hold-down force, and maintaining the right arm motionless to avoid artifacts (4). The reported intraobserver and interobserver variability for the described method are 4.5 ± 2.5% and 6.1 ± 3.5%, respectively (4).

**Echocardiography.** Two-dimensionally guided M-mode echocardiography was performed according to the conventions established by the American Society of Echocardiography (52) using a commercially available instrument (Sonos 5500, Hewlett Packard). The following parameters were measured over 3 cardiac cycles

from the parasternal short axis view: posterior wall thickness (PWTs, PWTd), ventricular septal wall thickness (VSTd, VSTs) and internal cavity dimensions (LVIDs, LVIDd). LV mass was derived from the formula described by Devereux et al. (16): LV mass (grams) = 0.80 [1.04 (VSTd + LVIDd + PWTd)$^3$ - (LVIDd)$^3$] + 0.6, where thickness and dimension measurements are expressed in centimeters and were indexed to body surface area (BSA = body weight (kg)$^{0.425}$ · height (cm)$^{0.725}$) · 0.007184). A echocardiographic technician performed all images. All echocardiographic examinations were recorded on a video tape. Image analysis was performed by a technician who was blinded to the treatment group.

**Treatment.** Treatment included 10 weeks of AT or CT performed 3 times per week on alternate days. All training sessions were supervised in the cardiovascular therapeutic exercise laboratory within the Faculty of Rehabilitation Medicine at the University of Alberta. AT initially consisted of 15 min of cycling on a Monark cycle ergometer at the individually determined intensity of 50 to 70% of heart rate reserve. For the first 5 weeks, exercise duration was increased by 2.5 min per week. For the second 5 weeks, subjects performed a combination of continuous interval training 2 times per week. The third weekly session consisted of continuous steady-state cycling for 35 min at 50 to 70% heart rate reserve. Continuous interval training consisted of 2 min of high intensity cycling at 85% heart rate reserve followed by 2 min of low intensity cycling at 50% heart rate reserve. The number of intervals was 5 for week 6, 6 for the weeks 7 and 8, and 7 for weeks 9 and 10.

RT included 8 resistance exercises: leg press, leg extension, leg curl, chest press, shoulder press, lat pull-down, arm curls and triceps pushdown. Following a warm-up set, subjects performed 2 sets of 10-15 repetitions at 50% to 65% of 1 RM

with 1-minute rest between sets. The initial weight for the 2 sets was 50% of 1 RM. The weight was increased by 5% to 10% every four weeks.

Subjects exercised 30 to 60 minutes per training session. The training time included 5 minutes of warm up and 5 minutes of cool down. The workload, duration, number of repetitions and heart rate were recorded in a training log for every training session.

**Statistical analysis.** One way ANOVA was used to compare baseline characteristics of subjects who completed versus those who dropped out from the study. The same analysis was used to compare and baseline characteristics of the subjects in AT and CT group. Two-factor (treatment by time) MANOVA was performed to determine the main effects of the treatment and time and a possible treatment by time interaction for major dependent variables including systolic and diastolic BP at rest, large and small AC, and LV mass index. An additional two-factor (group by time) MANOVA was performed on subgroups of normotensive and hypertensive subjects to determine if there is a different response to exercise in BP at rest, AC and LV morphology in diabetic women after controlling for hypertension. Separate MANOVAs (treatment by time and group by time) were performed to analyze measured hemodynamics and LV parameters that were not included in the hypotheses but were measured in the study. Statistical analyses were performed using SPSS 10.0 software. Effect sizes were calculated and reported for each measured parameter. Values of $P < 0.05$ were considered as statistically significant. Results are reported as mean ± standard deviation.

### 3.3 Results

Sixteen subjects were recruited for the study. One subject did not meet the inclusion criteria of the postmenopausal status and was excluded from the study.

Eligible subjects were randomly assigned to AT and CT group. Five subjects (3 from AT and 2 from CT group) dropped out from the study for personal reasons. Ten subjects completed the program (4 in AT, and 6 in CT). No subject reported a change in an amount or type of medications for the duration of the study.

**Compliance.** The subjects that completed the study participated in more than 70% of the planned exercise sessions (average, 80.3%; AT, 85.0%; CT, 77.2%). Comparison of baseline characteristics of subjects who completed versus those who dropped out from the study revealed significantly reduced $VO_{2\ 60\ watts}$ in the latter group (Table 3-1).

**Subjects characteristics.** Baseline subject characteristics of AT and CT groups are presented in Table 3-2. Although randomly assigned, subjects in AT group had higher heart rate at rest (85.8 ± 10.7 vs. 70.2 ± 13.3), higher $SBP_{60\ watts}$ (192.0 ± 22.7 vs. 166.3 ± 30.2), reduced large AC (6.2 ± 1.3 vs. 13.2 ± 4.2) (Table 3-2 and 3-3), and greater ventricular septal wall thickness in diastole (12.3 ± 1.9 vs. 9.2 ± 1.6) (Table 3-4) when compared to CT group. No difference between the groups was found for the other parameters.

### 3.3.1 Effects of AT and CT on BP, AC, and LV Morphology

Ten weeks of AT or CT did not alter baseline SBP and DBP at rest, AC, or LV morphology (Table 3-3). Results of MANOVA showed a non-significant main effect for time and time by treatment interaction for measured parameters. BP profile at rest and during exercise was not changed following 10 weeks of either exercise program (Table 3-3). Data analysis showed non-significant alterations in indices of AC. However, the AT group demonstrated a 32% increase in both large and small AC, but these changes did not reach statistical significance (Table 3-3). The echocardiographic data are shown in Table 3-4. LV systolic and diastolic internal

dimensions, posterior and septal ventricular wall thickness, and LV mass index were not significantly altered following 10 weeks of either AT or CT exercise intervention. In addition, neither group demonstrated significant changes in exercise capacity (Table 3-3). Oxygen consumption at a fixed exercise load was not changed following an exercise intervention while an increase in $VO_{2peak}$ of 6% in AT and 13% in CT group did not approach statistical significance (Table 3-3). These observations were supported with no change in heart rate at fixed exercise load (Table 3-3). All changes were observed independently of changes in body weight (AT: 92.0 (kg) ± 15.6 (pre), 89.6 ± 15.3 (post); CT: 97.8 ± 9.8 (pre), 96.8 ± 10.7 (post)).

### 3.3.2 Effects of an Exercise Intervention on BP, AC, and LV Morphology in Normotensive and Hypertensive Diabetic Patients

Comparison of hypertensive and normotensive subgroups in our study has revealed a significant main effect of hypertension on SBP at rest, $VO_{2peak}$ and $DBP_{60\ watts}$ (Table 3-5). Hypertensive patients had significantly higher SBP at rest, lower $VO_{2peak}$ and $DBP_{60\ watts}$ and tended to have lower $VO_{2\ 60\ watts}$ than normotensive individuals at the initial assessment. A main effect for time was not significant for any measured variable. SBP and DBP at rest and during exercise was not altered in either subgroup following 10 weeks of exercise. There was a significant group by time interaction for LV mass index (Table 3-5). The LV mass index decreased in a subgroup of hypertensive individuals (pre: 106.3 ± 28.7; post: 92.0±19.5), but increased in normotensive diabetic subjects (pre: 74.7 ± 16.0 vs. 113.4 ± 13.1).

## 3.4 Discussion

The purpose of this study was to evaluate the effects of 10 weeks of AT and CT on SBP and DBP at rest, AC, and LV morphology in sedentary postmenopausal women with NIDDM. The study also examined a response of these parameters to an

exercise intervention in subgroups of normotensive and hypertensive diabetic women. Results of this study suggest that sedentary postmenopausal women with NIDDM do not alter BP profile at rest, large and small AC, or LV morphology in response to 10 weeks of AT or CT intervention. In addition, normotensive and hypertensive diabetic women demonstrated similar BP and AC, but not LV morphology responses to an exercise intervention. In the present study, hypertensive diabetic women demonstrated a decrease in LV mass index while normotensive patients showed an increase in LV mass index in response to an exercise intervention. Finally, the results suggest that sedentary postmenopausal women with co-existence of NIDDM and hypertension have reduced exercise capacity compared to normotensive NIDDM individuals. These results should be interpreted cautiously due to a small sample size and absence of a non-exercising control group in the present study.

### 3.4.1 Effects of AT and CT on BP, AC, and LV Morphology

**Blood pressure.** Our sample of post-menopausal diabetic women did not demonstrate a change in SBP and/or DBP at rest following 10 weeks of either AT or combined exercise intervention. Previous studies have demonstrated antihypertensive effects of AT (5,65) but not circuit RT interventions in sedentary middle-aged and older diabetic patients (18,26). Beneficial effects of CT on SBP and DBP reduction have been reported in middle-aged sedentary hypertensive men (30). To our knowledge, this is the first study that reported the effects of AT and CT on SBP and DBP at rest and during exercise in sedentary post-menopausal women with NIDDM.

There are several possible explanations for our findings. Clinical BP measurement at only one occasion at the baseline and a follow up as performed in the present study may not provide accurate information about true BP profile in our subjects. In addition, daily BP was probably overestimated due to the elimination of

any potential effects of post-exercise hypotension (47). Ambulatory BP measurement and multiple clinical BP readings may provide better insight in the effects of exercise on BP profile (38) and should be considered in future studies. A recent review suggests that approximately 75% of hypertensive patients lower their BP in response to AT (22). The small sample size used in this study may be inadequate to account for the presence of non-responders to an exercise treatment and their presence may interfere with the observed results. Another possibility could be an inadequate training stimulus. AT intervention that induced significant decrease in SBP and DBP in NIDDM patients in previous studies consisted of at least 30 min of AT per training session, 3 times per week (38,53,65). In the present study subjects began with 15 min of cycling and progressed to 30 min per exercise session by week 5. Only 5 weeks of AT in duration of 30 min or longer may be insufficient to produce BP reduction in this population. Although previous studies reported that RT did not reduce BP at rest in hypertensive (23) and diabetic patients (18), a recent study demonstrated hypotensive effects of CT in middle-aged sedentary hypertensive men (30). Discrepancy of the effects of CT in the latter (30) and present study may be attributed to clinical characteristics of diabetic patients and/or gender differences. Previous studies suggest that antihypertensive effects of exercise depend on the initial BP level (17). However, a separate analysis of hypertensive and normotensive subgroups of NIDDM patients in the present study did not reveal a different response to exercise intervention between the two groups (Table 3-5). Another possibility is that BP response to an exercise intervention may be influenced by usage of antihypertensive medications and/or hormone replacement therapy. This explanation is unlikely since no difference in BP response to exercise intervention has been reported in users versus non-users of antihypertensive medications or hormone supplementation in

hypertensive post-menopausal women (54). Finally, beneficial effects of exercise on BP in diabetic patients may be attenuated due to presence of multiple CVD risk factors including hypertension, obesity and abnormal lipid profile, as well as impaired endothelial function, a higher degree of arterial stiffness, and presence of elevated LV mass.

The underlying mechanisms for an exercise-induced reduction in BP at rest and during exercise observed in previous studies remain unclear. Postulated mechanisms are likely multi-factorial and depend on the nature of hypertension and the individual's clinical characteristics (17). Exercise-induced reduction in SBP and DBP is ultimately associated with reduced total peripheral resistance, cardiac output, or both (36). Speculated mechanisms include an increased vascular vasodilation attributed to increased AC and/or improved endothelial function (17,24,32), attenuated sympathetic nervous system activity (17,21), and/or changes in insulin sensitivity and hyperinsulinemia (15,17). Some studies speculated a possible role for decreased plasma volume (36) and increased skeletal muscle capillary bed (32), but more data are required to support these mechanisms. Since no change in BP profile has been observed in the present study, we are unable to speculate the mechanisms involved in hypotensive effects of exercise.

**Arterial compliance.** In the present study, neither AT nor CT improved large and small AC in post-menopausal diabetic women (Table 3-3). Although the AT group demonstrated 32% increase in both large and small AC, these changes did not approach statistical significance. To date, only two studies examined the effects of an exercise intervention on AC. One study reported increased AC by 25 % in previously sedentary middle-aged and older healthy men following 12 weeks of AT intervention (initially: 25 to 30 min/d, 3 to 4 d/wk, 60% $HR_{max}$; increased to: 40 to 45 min/d, 4 to 6

d/wk, 70% to 75% $HR_{max}$) (61). Another study found increased total systemic AC following 4 weeks of AT in young men (30 min/d, 3 d/wk, 75% $VO_{2max}$) (11). To our knowledge, this is the first study that has examined the effects of AT and CT on AC in sedentary post-menopausal women with NIDDM.

There are several possible explanations for our findings. Although randomly assigned, subjects in the AT group had significantly lower baseline large AC than the CT group. Hence, an observed non-significant increase in large AC in AT group following an exercise intervention may be a consequence of the lower baseline levels and/or phenomena of the regression toward the mean. The effects of RT on AC, alone or in combination with an aerobic component, warrant further examination. There is a possibility that neither training stimulus was sufficient and/or adequate. A comparison of AT interventions used in the present and a previous study by Tanaka et al. (61) that reported increased AC in healthy men following 12 weeks of AT reveals lower exercise duration and frequency in our study while exercise intensity was comparable. Comparison with the study by Cameron et al. (11), however, shows similar exercise duration and frequency and slightly lower exercise intensity in the present study. Future studies need to determine an optimal exercise program for restoration of AC in diabetic patients. Further, an inherent measurement variability of the applanation tonometry technique for an assessment of AC cannot be ignored. Although special attention was devoted to avoid artifacts, a previously reported intraobserver (4.5 ± 2.5%) and interobserver variability (6.1 ± 3.5%) (4) may preclude differentiation of the effects of exercise since exercise-induced changes are most likely within the range of measurement error. Finally, the highest degree of arterial stiffness observed in patients with co-existent NIDDM and hypertension (70% of our sample) may require

a more aggressive treatment, including higher intensity and duration of exercise, to induce beneficial changes in AC.

Mechanisms for exercise-induced increase in AC observed in previous studies remain unclear. Speculated mechanisms may include an improved endothelial function (33,44), alteration of the connective tissue cross-linking by a "stretching" effect induced by an increased pulse pressure and mechanical distension during exercise (29), improved baroreflex sensitivity, a parameter that is strongly and positively related to AC (34), and/or inhibition of the sympathetic nervous system activity which modulates the smooth muscle cell tone in the arterial wall (42,43,61).

**Left ventricular morphology.** In this study of diabetic postmenopausal women, LV morphology was not altered following 10 weeks of either AT or CT. To date, three studies reported effects of an exercise intervention on LV morphology in sedentary middle-aged and older hypertensive men, while no similar data were reported for diabetic patients and/or women. The studies reported a decrease in LV mass index following 4 and 7 months of AT (35,63) and increased LV mass index without concomitant alteration in diastolic function following 10 weeks of CT (30).

Several reasons can be suggested for an observed discrepancy between previous and present studies in effects of AT and CT on LV morphology. A magnitude of LV mass reduction may depend on the initial LV mass. Studies that reported a reduction in LV mass following AT intervention were performed on patients with LV hypertrophy (LV mass index: >116 $g \cdot m^{-2}$ for men; >104 $g \cdot m^{-2}$ for women (8)) (35,63), while in the present study only 4 subjects had LV hypertrophy at the initial assessment. However, due to lack of randomization in one study (63), the results should not be extrapolated to all hypertensive patients. Further, presence of hyperinsulinemia in diabetic patients may have an impact on LV morphology

response to exercise intervention since improvement in hyperinsulinemia is one of the possible mechanisms involved body weight- and possibly exercise-induced LV mass reduction in obese hypertensive and normotensive subjects (25). Finally, the potential role of gender differences in response to exercise intervention should not be ignored.

Mechanisms involved in regression of LV hypertrophy in previous studies are not clear but may include reduction of SBP at rest (25,35), decrease in body weight (25), improvements in hyperinsulinemia (25), and involvement of angiotensin II and catecholamines (35).

### 3.4.2 Effects of an Exercise Intervention on BP, AC, and LV Morphology in Normotensive and Hypertensive Diabetic Patients

Co-existence of NIDDM and hypertension represent a particularly high risk for CVD morbidity and mortality (7,41,51,62). Although strong evidence suggests beneficial effects of exercise in diabetic and hypertensive patients, to our knowledge this is the first study that compared baseline characteristics and responses to an exercise intervention in NIDDM patients after controlling for the presence of hypertension. Our data suggests that normotensive and hypertensive diabetic women have similar BP and AC response, but not LV morphology response to an exercise intervention.

Although previous studies suggested that absolute BP reduction following antihypertensive therapy depends on the initial BP level (17) and presence of multiple CVD risk factors (46), we observed no different BP response to an exercise intervention in diabetic post-menopausal women after controlling for the presence of hypertension. Possible explanations for this finding may include different effects of two exercise treatments that were not taken into account in this sub-analysis and/or insufficient power to observe a change due to a small sample size in each group

(normotensive, n=3; hypertensive, n=7). The first explanation is unlikely because the present study did not demonstrate a difference between two exercise treatments on BP profile (Table 3-3). The second possibility is a limitation of this study and suggests that obtained results should be interpreted cautiously.

Response of AC to exercise intervention in diabetic and hypertensive patients has not been reported. Due to paucity of data available in this area of research, there is not enough evidence to expect a different AC response to exercise intervention in normotensive and hypertensive diabetic subjects.

A significant subgroup by time interaction for LV mass index was an unexpected finding. A decrease in LV mass index following exercise in a subgroup of hypertensive patients may be attributed to higher initial LV mass (Table 3-5) and/or presence of 4 subjects with LV hypertrophy who demonstrated the greatest decrease in LV mass index for the duration of the study. Conversely, an increase in LV mass index in normotensive subjects may be a consequence of the lower initial LV mass values and the phenomena of the regression toward the mean. Finally, the inadequacy of a small sample size to account for a great variation and possibility of measurement error cannot be excluded.

Impaired exercise capacity in NIDDM patients compared to the healthy age-matched controls has already been reported (10,49,50). Results of this study expand previous knowledge showing that the presence of hypertension has additional adverse effects on already reduced exercise capacity in diabetic women. This finding is consistent with an increased risk of CVD morbidity and mortality in patients with co-existence of NIDDM and hypertension. Since improvements in maximal exercise capacity with regular exercise have been reported in diabetic subjects (65), future

studies need to examine if these findings could be extended to diabetic subjects with hypertension.

### 3.4.3 Limitations

Major limitations of the present study were a small sample size and absence of non-exercising control group. In addition, single clinical BP measurement may be insufficient to detect changes in BP at rest following an exercise intervention. Finally, favorable effects of exercise on SBP and DBP at rest, AC and LV morphology in most (11,27,35,63,65) but not all studies (54,61) were associated with an improvement in cardiovascular fitness measured by $VO_{2\ peak}$. Absence of significant changes in cardiovascular fitness parameters such as $VO_{2\ peak}$ and $VO_2$ and heart rate at standard exercise load in the present study may be due to an insufficient training stimulus which may also be inadequate to generate favorable changes in the cardiovascular system of diabetic patients. However, although statistically nonsignificant, a 13% improvement in $VO_{2\ peak}$ following CT may have an important clinical implication for enhancing functional capacity and improving prognostic outcomes in this population. These limitations suggest that results of the present study should be interpreted cautiously.

### 3.4.4 Future directions

A larger study using an ambulatory BP measurement, multiple clinical BP readings, and a control group that will not receive an exercise treatment should evaluate the effects of exercise on BP, AC and LV morphology in diabetic women, particularly in the presence of hypertension. These patients often require multiple antihypertensive medications for effective BP control which burden them financially and increase a possibility of side effects and poor treatment compliance. Possible

beneficial effects of exercise on BP control may improve the quality of life in these patients.

Since decreased AC is evident even before the onset of hypertension (64), early detection of reduced AC even in normotensive individuals may improve prevention of CVD and provide a means for a better risk stratification (12,13). Future clinical practice should include measurements of AC and arterial wall abnormalities to identify individuals at high risk for cardiovascular events and to assess the effectiveness of therapeutic interventions, including exercise. Future studies should evaluate the effects of exercise on AC in women since menopause and hormone replacement therapy have been shown to have an independent effects on endothelial function (39,42) and thus may influence AC and its responses to an exercise intervention.

More research is required to evaluate the effects of RT, either alone or in combination with an aerobic component. Besides beneficial metabolic and functional effects of this training modality, an addition of RT to AT provides a more comprehensive exercise program for improvement of health, physical fitness and quality of life in NIDDM patients and may enhance poor long-term adherence to an exercise program in this population.

Finally, most studies on the effects of an exercise intervention on the cardiovascular system in diabetic and hypertensive patients have been done on men. However, unique CVD risk factors such as menopause and hormone replacement therapy in women suggests that data obtained on a male population may not necessarily be generalized to women. Therefore, future studies should determine to what extent beneficial effects of exercise observed in men may be generalized to women.

### 3.4.5 Conclusion

The present study demonstrated that 10 weeks of AT and CT did not alter SBP and DBP at rest, AC, and LV morphology in postmenopausal diabetic women. In addition, hypertensive diabetic women demonstrated a decrease in LV mass index while normotensive patients showed an increase in LV mass index in response to an exercise intervention. Finally, hypertensive diabetic women have a reduced exercise capaticy compared to normotensive diabetic individuals. A larger trial using postmenopausal diabetic women would be required to provide further clarification on this topic.

**Table 3-1.** Baseline characteristics of the subjects that completed and dropped out from the study

| | **Completed (n = 10)** | **Dropped out (n = 5)** |
|---|---|---|
| Age | 56.6 ± 6.2 | 53.6 ± 1.3 |
| Weight (kg) | 95.5 ± 12.0 | 88.9 ± 21.2 |
| BMI ($m^2 \cdot kg^{-1}$) | 35.3 ± 4.6 | 35.0 ± 5.9 |
| BSA ($m^2$) | 2.01 ± 0.13 | 1.90 ± 0.26 |
| SBP rest (mm Hg) | 141.1 ± 13.0 | 135.0 ± 19.8 |
| DBP rest (mm Hg) | 81.2 ± 7.8 | 77.8 ± 4.3 |
| $VO_{2peak}$ ($ml \cdot kg^{-1} \cdot min^{-1}$) | 19.5 ± 4.1 | 19.2 ± 6.3 |
| $VO_{2\ 60\ watts}$ ($ml \cdot kg^{-1} \cdot min^{-1}$) | 13.6 ± 1.3 | 16.7 ± 3.8* |
| Large AC ($ml \cdot mm\ Hg^{-1} \cdot 10$) | 10.9 ± 4.9 | 10.9 ± 3.8 |
| Small AC ($ml \cdot mm\ Hg^{-1} \cdot 100$) | 3.9 ± 3.0 | 3.1 ± 1.0 |

Data are mean ± SD. BMI indicates body mass index; BSA, body surface area; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; $VO_{2peak}$, peak oxygen consumption; $VO_{2\ 60\ watts}$, oxygen consumption at a fixed load of 60 watts; and AC, arterial compliance.

* $P<.05$ vs. subjects who completed the study

**Table 3-2.** Baseline characteristics of subjects in aerobic and combined aerobic and resistance training group

| | AT (n = 4) | CT (n = 6) |
|---|---|---|
| Age | 60.0 ± 8.3 | 54.3 ± 3.6 |
| Weight (kg) | 92.0 ± 15.6 | 97.8 ± 9.8 |
| BMI ($m^2 \cdot kg^{-1}$) | 34.2 ± 3.2 | 36.0 ± 5.4 |
| BSA ($m^2$) | 1.97 ± 0.19 | 2.04 ± 0.07 |
| HR rest (bpm) | 85.8 ± 10.7 | 70.2 ± 13.3† |
| SBP rest (mm Hg) | 152.8 ± 7.4 | 133.3 ± 9.6 |
| DBP rest (mm Hg) | 84.5 ± 3.5 | 79.0 ± 9.3 |
| $VO_{2peak}$ ($ml \cdot kg^{-1} \cdot min^{-1}$) | 20.5 ± 5.1 | 18.8 ± 3.6 |
| Large AC ($ml \cdot mm\ Hg^{-1} \cdot 10$) | 6.8 ± 1.7 | 13.2 ± 4.2† |
| Small AC ($ml \cdot mm\ Hg^{-1} \cdot 100$) | 3.1 ± 1.2 | 4.5 ± 3.2 |
| LVMI ($g \cdot m^{-2}$) | 110.1 ± 25.5 | 88.0 ± 30.0 |

Data are mean ± SD. BMI indicates body mass index; BSA, body surface area; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; $VO_{2peak}$, peak oxygen consumption; AC, arterial compliance; LVMI, left ventricular mass index; AT, aerobic training group; and CT, aerobic and resistance training group.

† $P<.05$ vs. aerobic training group

**Table 3-3.** Effects of aerobic and combined aerobic and resistance exercise intervention on hemodynamic parameters at rest and during exercise, arterial compliance, left ventricular mass, and exercise capacity

| | AT | | CT | | *Effect size* | |
|---|---|---|---|---|---|---|
| | **Pre** | **Post** | **Pre** | **Post** | ***Treatment*** | ***Time*** |
| $HR_{rest}$ | 85.8 ± 10.7 | 82.0 ± 15.5 | 70.2 ± 13.3† | 65.8 ± 7.7† | *.356* | *.032* |
| $SBP_{rest}$ | 152.8 ± 7.4 | 139.8 ± 16.8 | 133.3 ± 9.6 | 139.8 ± 21.4 | *.107* | *.013* |
| $DBP_{rest}$ | 84.5 ± 3.5 | 74.8 ±11.9 | 79.0 ± 9.3 | 77.2 ± 9.2 | *.009* | *.109* |
| $HR_{60\ watts}$ | 132.5 ± 14.4 | 129.3 ± 12.4 | 125.5 ± 19.5 | 113.7 ± 15.2 | *.129* | *.062* |
| $SBP_{60\ watts}$ | 192.0 ± 22.7 | 190.0 ± 12.0 | 166.3 ± 30.2† | 154.3 ± 27.5† | *.304* | *.022* |
| $DBP_{60\ watts}$ | 88.0 ± 14.0 | 81.5 ± 16.9 | 83.0 ± 8.7 | 81.8 ± 16.5 | *.008* | *.022* |
| $VO_{2\ 60\ watts}$ | 14.0 ± 1.3 | 14.2 ± 12.4 | 13.3 ± 1.3 | 13.5 ± 0.6 | *.065* | *.006* |
| $VO_{2\ peak}$ | 20.5±5.1 | 21.8 ± 5.8 | 18.8 ± 3.6 | 21.3 ± 5.1 | *.016* | *.044* |
| Large AC | 6.8 ± 1.7 | 9.0 ± 2.0 | 13.2 ± 4.2† | 13.2 ± 4.0† | *.422* | *.028* |
| Small AC | 3.1 ± 1.2 | 4.1 ± 1.5 | 4.5 ± 3.5 | 4.2 ± 2.9 | *.023* | *.006* |
| LVMI | 110.1 ± 25.5 | 105.6 ± 3.4 | 88.0 ± 30.0 | 93.7 ± 25.3 | *.129* | *.000* |

Data are mean ± SD. SBP, systolic blood pressure; DBP, diastolic blood pressure; $VO_{2peak}$, peak oxygen consumption; AC, arterial compliance; LVMI, left ventricular mass index; AT, aerobic training group; and CT, combined aerobic and resistance training group.

* $P<.05$ vs baseline; † $P<.05$ vs aerobic training group

**Table 3-4.** Effects of aerobic and combined aerobic and resistance exercise on left ventricular morphology

| | AT | | CT | |
|---|---|---|---|---|
| | **Pre** | **Post** | **Pre** | **Post** |
| LVIDd (mm) | 48.0 ± 4.4 | 48.0 ± 3.1 | 53.31 ± 7.8 | 49.1 ± 6.9 |
| LVIDs (mm) | 30.9 ± 7.5 | 30.4 ± 6.9 | 30.7 ± 6.7 | 32.1 ± 6.5 |
| VSTd (mm) | 12.3 ± 1.9 | 12.0 ± 8.0 | 9.2 ± 1.6† | 10.4 ± 0.9† |
| VSTs (mm) | 14.4 ± 2.1 | 13.2 ± 1.0 | 12.0 ± 1.5 | 12.5 ± 1.1 |
| PWTd (mm) | 11.5 ± 2.4 | 11.0 ± 0.4 | 9.0 ± 1.9 | 10.4 ± 0.6 |
| PWTs (mm) | 13.6 ± 2.2 | 12.5 ± 0.6 | 12.6 ± 1.9 | 12.4 ± 0.9 |
| RWT | 0.48 ± 0.10 | 0.46 ± 0.04 | 0.34 ± 0.09 | 0.43 ± 0.07 |
| LVM (g) | 220.7 ± 74.2 | 206.4 ± 27.4 | 180.9 ± 66.4 | 189.5 ± 47.6 |
| LVMI ($g \cdot m^{-2}$) | 110.1 ± 25.2 | 105.6 ± 3.4 | 88.0 ± 30.0 | 93.7 ± 25.3 |

Data are mean ± SD. LVIDd indicates left ventricular internal cavity dimension in diastole; LVIDs, left ventricular internal cavity dimension in systole; VSTd, ventricular septal wall thickness in diastole; VSTs, ventricular septal wall thickness in systole; PWTd, posterior wall thickness in diastole; PWTs, posterior wall thickness in systole; RWL, relative wall thickness; LVM, left ventricular mass; LVMI, left ventricular mass index; AT, aerobic training group; and CT, combined aerobic and resistance training group.

* $P<.05$ vs baseline

† $P<.05$ vs aerobic training group

**Table 3-5.** Effects of an exercise intervention on blood pressure at rest and during exercise, arterial compliance, left ventricular mass, and exercise capacity in subgroups of hypertensive and normotensive subjects

| | Normotensive | | Hypertensive | | *Effect size* | |
|---|---|---|---|---|---|---|
| | **Pre** | **Post** | **Pre** | **Post** | ***Group*** | ***Time*** |
| SBP rest | 131.7 ± 14.6 | 126.7 ± 9.3 | 145.1 ± 11.0† | 145.4 ± 19.2† | *.236* | *.007* |
| DBP rest | 81.3 ± 2.5 | 74.0 ± 12.8 | 81.1 ± 9.4 | 77.1 ± 9.2 | *.007* | *.089* |
| $SBP_{60\ watts}$ | 170.7 ± 25.3 | 172.0 ± 26.1 | 179.1 ± 32.3 | 167.1 ± 31.2 | *.001* | *.008* |
| $DBP_{60\ watts}$ | 91.3 ± 8.1 | 94.0 ± 14.0 | 82.3 ± 11.0† | 76.4 ± 14.0† | *.235* | *.004* |
| Large AC | 12.1 ± 6.3 | 12.9 ± 3.9 | 10.3 ± 4.6 | 10.9 ± 4.0 | *.052* | *.010* |
| Small AC | 5.2 ± 5.3 | 3.2 ± 1.3 | 3.2 ± 1.1 | 4.6 ± 2.6 | *.001* | *.006* |
| LVMI | 74.7 ± 16.0 | 113.4 ± 13.1 | 106.3 ± 28.7 | 92.0 ± 19.5† | *.012* | *.075* |
| $VO_{2peak}$ | 23.1 ± 3.8 | 27.0 ± 2.2 | 18.0 ± 3.3† | 19.1 ± 3.9† | *.473* | *.123* |

Data are mean ± SD. SBP, systolic blood pressure; DBP, diastolic blood pressure; AC, arterial compliance; LVMI, left ventricular mass index; BSA, body surface area; and $VO_{2peak}$, peak oxygen consumption.

* $P<.05$ vs baseline

† $P<.05$ vs normotensive group

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## Chapter 4

## General Discussion and Conclusions

An increased risk of morbidity and mortality in diabetic patients is at least in part attributable to the cardiovascular abnormalities such as decreased arterial compliance (AC) (25) and left ventricular hypertrophy (LVH) (8) that are further exacerbated in the presence of elevated blood pressure (BP) (3). Decreased AC accompanied with aging and hypertension may be a potent stimulus for the development of LVH (4).

Although regular physical activity including both aerobic (AT) and resistance exercise (RT) is emphasized in the treatment of this population (1), the effects of combined aerobic and resistance training (CT) have not been studied in diabetic individuals. Previous studies reported reduced systolic (SBP) and diastolic blood pressure (DBP) after AT (2,17,23,30) but not RT (7,12) interventions in diabetic patients. Increased AC has been found following AT in healthy sedentary men (5,15,27). Regression of LVH following AT (16,28) but not CT (14) has been reported in hypertensive men. Potentially beneficial effects of exercise on SBP, DBP, AC, and left ventricular (LV) morphology in diabetic women may decrease the rate of morbidity and mortality from cardiovascular disease (CVD), reduce costs to the health care system, and improve quality of life in this population.

Results in Chapter 3 suggest that 10 weeks of AT or CT do not alter SBP and DBP at rest, AC and LV morphology in diabetic postmenopausal women. In addition, LV mass changes in response to an exercise intervention may depend on the presence of hypertension in these patients. Finally, the presence of hypertension further impairs exercise capacity in postmenopausal diabetic women. The small sample size, lack of a

non-exercising control group, presence of non-responders, absence of ambulatory BP measurements and multiple clinical BP readings, and presence of multiple CVD risk factors are some of the possible explanations for the observed results. In addition, absence of changes in SBP, DBP, AC, and LV morphology in the present study may be attributed to the insufficient training stimulus that failed to improve exercise capacity in these patients. Although most (5,13,16,28,30) but not all (24)(27) exercise intervention studies reported favorable changes in BP, AC, and LV mass accompanied with 10% to 20% increase in maximal exercise capacity, a relation between an improvement in maximal exercise capacity and alterations in these parameters in diabetic patients remain to be determined. Due to importance of CT for an improvement of health, physical fitness, and quality of life in diabetic women, the effects of this type of training on SBP, DBP, AC, and LV morphology should be reexamined in a larger clinical trial.

More recently, the importance of endothelial function in the incidence of cardiovascular events has been recognized (20). Impaired endothelial function that may precede the development of arterial stiffness (26) and LVH (21) has been found in diabetic (19,29) and hypertensive patients (10). A potential role of exercise in both prevention (6,22) and restoration (6,9-11,18) of age- or disease-related endothelial dysfunction has also been reported. AT improved endothelial function in healthy sedentary individuals (6,10), as well as in patients with hypertension (10,11) and coronary artery disease (9), while favorable effects of moderate intensity CT have been reported in diabetic patients (18). Improvement in endothelial function may precede an exercise-induced alteration in AC and LV morphology, and should be examined in the future studies along with the measurements of SBP, DBP, AC, and LV parameters.

In conclusion, in addition to adequate BP control, increased AC, regression of LVH, and improved endothelial function should represent new targets for therapeutic interventions in diabetic patients. The beneficial effects of exercise, particularly CT, in prevention and restoration of these cardiovascular abnormalities in diabetic women need further investigation. Future studies should also examine possible additive effects of pharmacological, dietary, and exercise interventions to determine an optimal treatment for these patients.

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